http://dx.doi.org/10.1016/j.hpb.2017.06.008 HPB

ORIGINAL ARTICLE

Impact of adjuvant chemotherapy on survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis

Bradley N. Reames[1*], Fabio Bagante[2*], Aslam Ejaz[1], Gaya Spolverato[2], Andrea Ruzzenente[2], Matthew Weiss[1], Sorin Alexandrescu[3], Hugo P. Marques[4], Luca Aldrighetti[5], Shishir K. Maithel[6], Carlo Pulitano[7], Todd W. Bauer[8], Feng Shen[9], George A. Poultsides[10], Oliver Soubrane[11], Guillaume Martel[12], Bas G. Koerkamp[13], Alfredo Guglielmi[2], Endo Itaru[14] & Timothy M. Pawlik[15]

[1]Department of Surgery, Johns Hopkins Hospital, Baltimore, MD, USA, [2]Department of Surgery, University of Verona, Verona, Italy, [3]Department of Surgery, Fundeni Clinical Institute, Bucharest, Romania, [4]Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal, [5]Department of Surgery, Ospedale San Raffaele, Milan, Italy, [6]Department of Surgery, Emory University, Atlanta, GA, USA, [7]Department of Surgery, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia, [8]Department of Surgery, University of Virginia, Charlottesville, VA, USA, [9]Department of Surgery, Eastern Hepatobiliary Surgery Hospital, Shanghai, China, [10]Department of Surgery, Stanford University, Stanford, CA, USA, [11]Department of Hepatobiliopancreatic Surgery and Liver Transplantation, AP-HP, Beaujon Hospital, Clichy, France, [12]Division of General Surgery, Department of Surgery, University of Ottawa, Ottawa, ON, Canada, [13]Department of Surgery, Erasmus University Medical Centre, Rotterdam, The Netherlands, [14]Gastroenterological Surgery Division, Yokohama City University School of Medicine, Yokohama, Japan, and [15]Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

Abstract

Background: The benefit of adjuvant chemotherapy for resected intrahepatic cholangiocarcinoma (ICC) is unclear. The aim of the current study was to investigate the impact of adjuvant chemotherapy on survival among patients undergoing resection of ICC using a multi-institutional database.

Methods: 1154 ICC patients undergoing curative-intent hepatectomy between 1990 and 2015 were identified from 14 institutions. Cox proportional hazard modeling was used to determine the impact of adjuvant chemotherapy on overall survival (OS).

Results: Following resection, 347 (30%) patients received adjuvant chemotherapy, most commonly a gemcitabine-based regimen (n = 184, 52%). Patients with T2/T3/T4 disease were more likely to receive adjuvant therapy compared with patients with T1a/T1b disease (OR 2.5, 95%CI 1.89–3.23; P < 0.001). Among patients who did and did not receive adjuvant therapy, patients with T2/T3/T4 tumors had a 5-year OS of 37% (95%CI 28.9–44.4) versus 30% (95%CI 23.8–35.6), respectively (p = 0.006). Similarly patients with N1 disease who received adjuvant chemotherapy tended to have improved 5-year OS (18.3%, 95%CI 9.0–30.1 vs. no adjuvant therapy 12%, 95%CI 3.9–24.4; P = 0.050).

Conclusions: While adjuvant chemotherapy did not influence the prognosis of all ICC patients following surgical resection, it was associated with a potential survival benefit in subgroups of patients at increased risk for recurrence, such as those with advanced tumors.

Received 20 April 2017; accepted 14 June 2017

Correspondence

Timothy M. Pawlik, Department of Surgery, The Urban Meyer III and Shelley Meyer Chair for Cancer Research, The Ohio State University, Wexner Medical Center, 395 W. 12th Ave., Suite 670, USA. E-mail: Tim.Pawlik@osumc.edu

National presentation: This work was presented as a long oral presentation at the Americas Hepato-Pancreato-Biliary Association Annual Meeting in Miami, FL, on April 1st, 2017.

*These authors contributed equally to this work.

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.

Introduction

Over recent decades, the incidence and mortality of intrahepatic cholangiocarcinoma (ICC) has dramatically increased both in the United States and worldwide.[1–4] Patients with unresectable ICC have a 5-year survival of 5–10%, and only a minority of patients are candidates for surgery.[5] Even attempts at curative-intent resection are associated with poor outcomes, with estimated overall 5-year survival of 25–30%.[1,6–8] The poor long-term prognosis of patients with ICC is related, in part, to the high incidence of recurrence. In fact, up to 70% of patients have been reported to develop a recurrence within 2 years of surgery.[9] While the most common site for initial recurrence after resection of ICC is intrahepatic, up to 50% of patients will develop extrahepatic disease.[10] In addition, when recurrence occurs prognosis is usually poor.

Given the generally poor outcomes following surgery alone for patients with ICC, systemic therapy is frequently considered in the adjuvant setting. Current national guidelines recommend adjuvant chemotherapy only for patients with residual disease or nodal metastasis. In contrast, recommendations for patients who undergo a margin-negative, node-negative resection are ambiguous, and include observation, clinical trials, or consideration of adjuvant chemotherapy.[11,12] Given the relative rarity of ICC, evidence to support the use of adjuvant chemotherapy has been extrapolated from phase II trials of mixed hepatobiliary malignancies or retrospective small single institutional series of ICC patients.[5,13–15] The main phase III trial on the use of systemic therapy for advanced biliary malignancies investigated the use of gemcitabine mono-therapy versus doublet therapy with gemcitabine plus cisplatin.[16] However, this trial included patients with advanced inoperable disease who were not surgical candidates. Recently, two randomized clinical trials presented at the 2017 American Society of Clinical Oncology (ASCO) annual meeting reported different conclusions. Specifically, in a study examining Gemox versus surveillance following surgery of localized biliary tract cancer, the authors reported the results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. This study concluded that adjuvant chemotherapy for biliary tract cancer with GEMOX was feasible and associated with expected toxicities and no deterioration of health-related quality of life (HrQoL); however, there were no significant differences in recurrence-free survival between Gemox and surveillance.[17] In contrast, in another study investigating adjuvant capecitabine for biliary tract cancer in the BILCAP randomized trial, the authors reported that capecitabine improved overall survival for biliary tract cancer when used as an adjuvant therapy.[18] Whether these data are relevant to the adjuvant setting remains unknown.

In current clinical practice, commonly used therapies for ICC in the adjuvant setting include cisplatin-, gemcitabine-, or fluoropyrimidine-based regimens.[11,13,15,16] The benefit of adjuvant chemotherapy following curative-intent hepatectomy remains, however, poorly understood, and consequently is often subject to national norms and provider or institutional preferences. Therefore, the objective of the current study was to characterize the overall pattern of utilization of adjuvant therapy among a large cohort of patients who underwent curative-intent resection of ICC. Specifically, the study sought to define the survival benefit associated with adjuvant chemotherapy following hepatectomy for ICC, as well as identify specific subsets of patients who may benefit the most from adjuvant chemotherapy.

Materials and methods

Study population and data collection

Patients undergoing curative-intent hepatectomy for histologically confirmed ICC between the years 1990 and 2015 were identified from a multi-institutional database from 14 major hepatobiliary centers in North America, Europe, Australia, and Asia (Supplementary Table 1). Cholangiocarcinoma with a significant intrahepatic component with or without a direct involvement of the confluence were defined as ICC. Intrahepatic mass lesions with hilar duct involvement were excluded from the study when the center of the liver mass was located between the right side of the umbilical portion of the left portal vein and the left side of the right posterior portal.[19,20]

Demographic variables were collected including age, gender, American Society of Anesthesiologist (ASA) score and BMI. Relevant clinical variables included preexisting hepatobiliary disease, presence of jaundice or cirrhosis, extent of malignancy in liver, and receipt (and type) of systemic therapy. Operative details included type and extent of hepatectomy, associated procedures (vascular resection, bile duct resection, margin re-resection) performance of lymphadenectomy, operative time, and estimated blood loss. Histopathologic tumor characteristics included size, number of lesions, lymph node involvement, margin status, histological grade, morphologic type, perineural, biliary, or vascular invasion, and extension to other organs. Institution specific final histopathological reports were used to determine nodal and margin status and variables within the database (AJCC staging and tumor characteristics) were standardized across institutions as well as throughout the study period. Major hepatectomy was defined as the resection of three or more liver segments according to Couinaud's classification.[21] Tumor stage was classified using the American Joint Committee on Cancer (AJCC) 8th edition staging system.[22]

Primary outcomes and statistical analysis

The primary outcome was overall survival (OS), which was calculated from the date of surgery. Descriptive statistics were calculated using Student's t-test, Wilcoxon rank sum, or Chi-square tests, as appropriate for normally or non-normally distributed data. OS time was calculated using the Kaplan–Meier method and compared between the two patient groups

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.

using the logrank test. Univariable and multivariable logistic regression analyses were used to identify predictors of adjuvant chemotherapy use. Variables that had a P-value <0.1 on univariable analyses were included in the final multivariable model. Multivariable cox regression analysis was used to examine the impact of adjuvant chemotherapy on overall survival, after adjusting for demographic, clinical, operative, and pathologic characteristics. All analyses were performed using STATA version 12 (StataCorp, College Station, TX), with two-sided tests and alpha set at 0.05. The institutional review board of each participating institution approved the study protocol.

Results

Patient characteristics

Among the 1209 patients identified, patients who underwent a palliative procedure (n = 5) and patients without operative details (n = 50) were excluded, leaving 1154 ICC patients who underwent curative-intent resection in the analytic cohort. Differences in demographic, clinical, operative, and pathologic characteristics among the entire cohort, and in patients who did versus did not receive adjuvant chemotherapy are described in Tables 1a and 1b. Characteristics of adjuvant therapy for the entire cohort are listed in Table 2. While 149 (43%) patients received single agent chemotherapy and 187 (54%) had two agents, only a minority (n = 11, 3%) received a combination of three or more drugs. Independent factors associated with receipt of adjuvant chemotherapy are shown in Table 3.

Adjuvant chemotherapy and AJCC staging system 8th edition

Patients with T2/T3/T4 disease remained roughly twice as likely to receive adjuvant therapy compared with patients who had T1a/T1b disease (OR 2.5, 95%CI 1.89–3.23; P < 0.001). Of note, while the presence of N1 disease was associated with a slightly increased odd of receiving adjuvant therapy compared with N0 disease (OR 1.47, 95%CI 0.93–2.35; P = 0.10), NX patients were less likely to receive adjuvant therapy compared with N0 patients (OR 0.52, 95%CI 0.35–0.78; P < 0.001). Of note, independent of clinical factors, adjuvant therapy administration did not increase across the time periods examined (reference, 1990–1999: 1999–2010, OR 0.75, 95%CI 0.36–1.54 vs. 2006–2015, OR 0.64, 95%CI 0.31–1.31; both P > 0.20).

Table 1a Clinical characteristics of patients with Intrahepatic Cholangiocarcinoma undergoing curative-intent resection (n = 1154)

Variables	Entire Cohort N (%)[a]	Non-Chemotherapy N (%)[b]	Chemotherapy N (%)[b]	p-value
Patients	1154	807 (70)	347 (30)	–
Age, median (IQR)	60 (52–69)	60 years (51–69)	61 years (53–68)	0.84
Gender				0.002
Female	516 (45)	336 (65)	180 (35)	
Male	638 (55)	471 (74)	167 (26)	
ASA				<0.001
1–2	634 (55)	480 (76)	154 (24)	
3–4	520 (45)	327 (63)	193 (37)	
Cirrhosis				<0.001
No	1036 (90)	750 (72)	286 (28)	
Yes	118 (10)	110 (93)	8 (7)	
HBV infection				<0.001
No	949 (82)	669 (71)	280 (29)	
Yes	205 (18)	181 (88)	24 (12)	
HCV infection				0.033
No	1123 (97)	843 (75)	280 (25)	
Yes	31 (3)	18 (58)	13 (42)	
Neoadjuvant chemotherapy				<0.001
No	1070 (93)	809 (76)	261 (24)	
Yes	84 (7)	41 (49)	43 (51)	
Ca 19-9, median (IQR)	49 (17–204)	40 (16–154)	90 (22–300)	<0.001

[a] Column percentage.
[b] Row percentage.

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.

Table 1b Pathologic characteristics of patients with Intrahepatic Cholangiocarcinoma undergoing curative-intent resection (n = 1154)

Variables	Entire Cohort N (%)[a]	Non-Chemotherapy N (%)[b]	Chemotherapy N (%)[b]	p-value
Patients	1154	807 (70)	347 (30)	–
Morphological type				<0.001
MF, IG	941 (82)	685 (73)	256 (27)	
PI, MF + PI	142 (18)	67 (47)	75 (53)	
Margin status				0.019
R0	992 (87)	706 (71)	286 (29)	
R1	146 (13)	90 (62)	56 (38)	
Tumor size				0.014
≤5 cm	451 (39)	334 (74)	117 (26)	
>5 cm	703 (61)	473 (67)	230 (33)	
Liver capsule involvement				<0.001
No	945 (82)	688 (73)	257 (27)	
Yes	209 (18)	119 (57)	90 (43)	
Direct invasion adjacent organs				0.15
No	1088 (94)	768 (71)	320 (29)	
Yes	66 (6)	41 (62)	25 (38)	
Major vascular resection				<0.001
No	1020 (88)	736 (72)	284 (28)	
Yes	134 (12)	71 (53)	63 (47)	
Bile duct resection				<0.001
No	851 (74)	627 (74)	224 (26)	
Yes	184 (26)	101 (55)	83 (45)	
Grade				<0.001
Well/moderate	884 (83)	643 (73)	241 (27)	
Poorly/undifferentiated	188 (17)	104 (55)	84 (45)	
Microvascular invasion				<0.001
No	771 (69)	575 (75)	196 (25)	
Yes	356 (31)	215 (60)	141 (40)	
Perineural invasion				<0.001
No	805 (79)	594 (74)	211 (26)	
Yes	217 (21)	114 (53)	103 (47)	
Pathological node status				<0.001
Negative	315 (27)	192 (61)	123 (39)	
Positive	200 (17)	104 (52)	96 (48)	
Not harvested	639 (56)	511 (80)	128 (20)	
Satellite lesion				0.12
No	905 (78)	642 (71)	263 (29)	
Yes	249 (22)	164 (66)	85 (34)	
Intrahepatic metastasis				0.019
No	1075 (93)	761 (71)	314 (29)	
Yes	79 (7)	46 (58)	33 (42)	
AJCC 8th edition T stages				<0.001
T1a	249 (22)	207 (83)	42 (17)	
T1b	270 (23)	208 (77)	62 (23)	
T2	402 (34)	260 (65)	142 (35)	
T3	167 (15)	91 (55)	76 (45)	
T4	66 (6)	41 (62)	25 (38)	

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.

Table 1b (*continued*)

Variables	Entire Cohort N (%)[a]	Non-Chemotherapy N (%)[b]	Chemotherapy N (%)[b]	p-value
AJCC 8th edition N stages				<0.001
N0	117 (10)	72 (62)	45 (38)	
N1	200 (17)	104 (52)	96 (48)	
NX	837 (73)	631 (75)	206 (25)	
AJCC 8th edition stages				0.19
Ia	15 (5)	12 (80)	3 (20)	
Ib	18 (6)	9 (50)	9 (50)	
II	37 (13)	17 (46)	20 (54)	
IIIa	22 (7)	14 (64)	8 (36)	
IIIb	204 (69)	108 (53)	96 (47)	

MF, mass-forming; IG, intraductal growth; PI, periductal infiltrating; MF + PI, mass-forming and periductal infiltrating.
[a] Column percentage.
[b] Row percentage.

Overall survival

Median OS was 3.2 years (95%CI: 1.3-NA) with 1-, 3-and 5-year OS of 81%, 52%, and 40%, respectively. Independent factors associated with survival are shown in Table 4. The effect of adjuvant chemotherapy on OS was then examined according to a number of technical and biologic risk factors (Supplementary Table 2). Interestingly, among patients with an R1 surgical margin the receipt of adjuvant chemotherapy was not associated with a 5-year survival benefit (5-year OS: no-chemotherapy, 24%, 95%CI 13.1–36.1 vs. chemotherapy 32%, 95%CI 18.5–46.4; p = 0.19) (Figure S1). In contrast, patients with other high-risk biologic features did derive a benefit from chemotherapy. Specifically, among patients with T2-T3-T4 tumors, 5-year OS was 37% (95%CI, 28.9–44.4) versus 30% (95%CI, 23.8–35.6) among patients who did and did not receive adjuvant therapy, respectively (p = 0.006) (Fig. 1a). Similarly, patients who had an ICC tumor with a PI/MF + PI morphological subtype derived a marked benefit from chemotherapy (5-year OS: no-chemotherapy, 37%, 95%CI 24.8–48.8 vs. chemotherapy 8%, 95%CI 0.9–25.0; p < 0.001) (Fig. 1b). Among patients with N1 disease, patients who received adjuvant chemotherapy tended to have a better 5-year OS (adjuvant therapy: 18%, 95%CI 9.0–30.1 vs. no adjuvant therapy: 12%, 95%CI 3.9–24.4; P = 0.050) (Fig. 1c). In fact, on cox regression analysis, the association between adjuvant chemotherapy and improved survival was strongest among patients with T3/T4 tumors (0.437, 95%CI 0.236–0.808, P < 0.01) and N1 disease (HR 0.244, 95%CI 0.130–0.457, P < 0.001), however patients with positive surgical margins did not seem to benefit (HR 0.578, 95%CI 0.259–1.29, P = 0.18). A sensitivity analysis was performed excluding patients lost at the follow-up during the first year after surgery to avoid the possibly confounding effect on the survival of patients in the adjuvant chemotherapy group with an inadequate follow-up. The sensitivity analyses confirmed the same association of adjuvant therapy with long-term outcome (Table S2, Figures S2–S6).

Table 2 Characteristics of adjuvant therapy

Variables	N (%)
Adjuvant treatment	
No	704 (61)
Yes	450 (39)
Type of treatment	
Chemotherapy alone	271 (60)
Tace alone	94 (21)
Radiotherapy alone	9 (2)
Chemo and radiotherapy	49 (11)
Chemo and radiotherapy and TACE	27 (6)
Adjuvant chemotherapy	
No	807 (70)
Yes	347 (30)
Gemcitabine based	
No	163 (48)
Yes	184 (52)
Platinum based	
No	203 (59)
Yes	144 (41)
5-FU based	
No	263 (75)
Yes	88 (25)

Discussion

The current study demonstrates that adjuvant chemotherapy does not appear to benefit all patients who undergo resection of ICC. Perhaps more importantly, adjuvant chemotherapy was associated with a decreased risk of death long-term among patients with certain pathologic features. Specifically, the benefit of

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.

Table 3 Multivariable logistic regression associated with receipt of adjuvant chemotherapy in patients with intrahepatic cholangiocarcinoma undergoing curative-intent resection

Variables	OR	95%CI	P-value
Liver capsule involvement			0.001
No	–	–	
Yes	1.91	1.30–2.81	
Vascular resection			<0.001
No	–	–	
Yes	1.94	1.35–2.78	
Intrahepatic metastasis			0.066
No	–	–	
Yes	1.72	0.96–3.08	
Grade			0.004
Well – moderate	–	–	
Poor – undifferentiated	1.79	1.20–2.68	
Perineural invasion			0.002
Not present	–	–	
Present	1.97	1.25–2.79	
Pathological nodal status			
Negative	–	–	–
Positive	1.05	0.66–1.67	0.83
Not harvested	0.47	0.32–0.69	<0.001
Morphological types			0.001
MF/IG	–	–	
PI/MF + PI	2.07	1.34–3.19	

MF, mass-forming; IG, intraductal growth; PI, periductal infiltrating; MF + PI, mass-forming and periductal infiltrating.

Table 4 Cox proportional hazards analysis for associations between survival and the specified variable in patients with intrahepatic cholangiocarcinoma undergoing curative-intent resection

Variables	HR	95%CI	P-value
Invasion of adjacent organs			<0.001
No	–	–	
Yes	1.86	1.37–2.54	
Margins			0.020
Negative	–	–	
Positive	1.36	1.04–1.76	
Tumor size			<0.001
≤5 cm	–	–	
>5 cm	1.82	1.49–2.22	
Lesion			<0.001
Unifocal	–	–	
Multifocal	1.47	1.19–1.83	
Grade			<0.001
Well – moderate	–	–	
Poor – undifferentiated	1.71	1.37–2.15	
Perineural invasion			0.013
Not present	–	–	
Present	1.36	1.07–1.72	
Pathological nodal status			<0.001
Negative	–	–	
Positive	2.48	1.88–3.26	
Not harvested	1.52	1.21–1.92	
Morphological types			<0.001
MF/IG	–	–	
PI/MF + PI	1.64	1.26–2.11	
Adjuvant chemotherapy			<0.001
Not performed	–	–	
Performed	0.60	0.49–0.74	

MF, mass-forming; IG, intraductal growth; PI, periductal infiltrating; MF + PI, mass-forming and periductal infiltrating.

adjuvant therapy was most pronounced among patients with more adverse prognostic features such as advanced T stage, the Periductal Infiltrating or Mass-forming and Periductal Infiltrating morphological subtype, and lymph node metastasis.

Adjuvant therapy was utilized in 39% of patients undergoing curative-intent resection for ICC. Receipt of adjuvant therapy was associated with certain clinicopathologic characteristics. For example, while ICC tumor size and surgical margin status were not associated with receipt of adjuvant therapy, Periductal Infiltrating or Mass-forming and Periductal Infiltrating morphological types, perineural invasion, vascular resection, liver capsule involvement, intrahepatic metastasis, and poorly-undifferentiated ICC did impact the likelihood of a patient to receive post-operative therapy. These data are consistent with the expectation that patients with more advanced disease would be more likely to be offered adjuvant therapy. However, it is important to note that the utilization of adjuvant chemotherapy was less than 50% even among high-risk patients. For example, while previous studies have demonstrated that lymph node metastasis was one of the strongest predictors of adverse long-term outcomes following resection of ICC, less than one-half of N1 patients received adjuvant therapy.[23,24] In contrast, patients with Periductal Infiltrating or Mass-forming and Periductal Infiltrating ICC morphological subtypes had the highest incidence of adjuvant chemotherapy (53%).

Prospective data on the benefit of adjuvant systemic therapy among patients with resected ICC are limited.[25] Two randomized trials of adjuvant chemotherapy that included patients with ICC did not demonstrate a difference in long-term survival comparing patients who underwent surgery-alone versus surgery plus adjuvant therapy.[26,27] The results of these studies are difficult to interpret, however, as both reports included patients with a wide variety of biliary tract malignancies. In the current study, adjuvant therapy was not associated with a survival benefit when the entire cohort was analyzed. Importantly, adjuvant therapy

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.

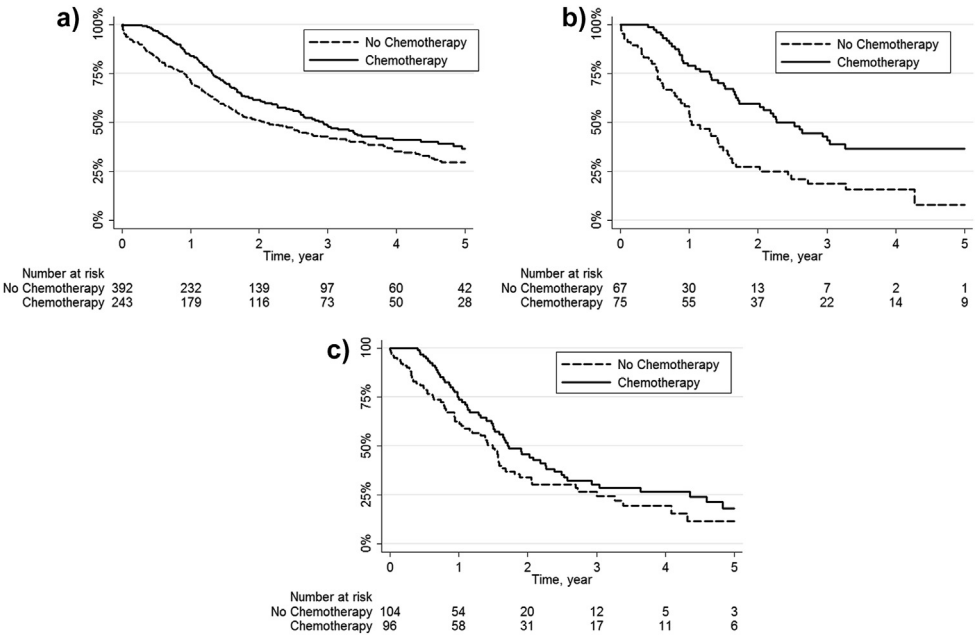

Figure 1 Kaplan Meier graph comparing patients who underwent adjuvant chemotherapy with patients who did not receive adjuvant chemotherapy in a) T2/T3/T4 stages, b) Periductal Infiltrating or Mass-forming and Periductal Infiltrating types, and c) N1 patients

was associated with a survival benefit in specific subsets of patients with high-risk features (Fig. 1a–c). Using data from the National Cancer Database, Miura et al. had similarly reported no difference in median OS following resection of ICC among the observation versus chemotherapy groups (23 vs. 20 months, P = 0.09).[28] However, the authors did note a survival benefit among subgroups of patients with N1 disease (19.8 vs. 10.7 months, P < 0.001) and T3/T4 tumors (21.3 vs. 15.6 months, P < 0.001). In a separate systematic review, Horgan et al. reported no improvement in survival associated with adjuvant therapy overall (OR 0.75, 95%CI 0.55–1.01, P = 0.06), yet did note a benefit among patients with N1 disease (OR 0.49, 95%CI 0.30–0.80, P = 0.004).[29] Collectively, these data strongly suggest that while the benefit of adjuvant therapy may only be modest when all patients with ICC are treated, certain high-risk subgroups may indeed derive a survival advantage from post-operative systemic treatment.

In the current study, while patients with lymph node metastasis (N1) did not have an increased likelihood to receive adjuvant chemotherapy (OR 1.05, p = 0.83), patients who did not undergo lymphadenectomy (NX) did have a much lower chance to receive chemotherapy (OR 0.47, p < 0.001) compared with node negative patients. The lower chance to receive adjuvant therapy among NX patients was interesting, as the presence of lymph node metastasis is one of the most important predictors of survival.[12,30–34] The routine performance of lymphadenectomy for ICC remains controversial, however, with different centers reporting variable rates of lymphadenectomy.[12,30,35–37] Although the evidence to suggest a survival benefit for lymphadenectomy is varied,[34,35,37,38] accurate nodal staging may assist in informing post-operative treatment. In particular, data from the current study demonstrated that adjuvant chemotherapy tended to be associated with a survival benefit among patients with N1 disease. In fact, patients with N1 disease who received adjuvant therapy had a decreased risk of death at 5-years compared with N1 patients who were simply observed following surgery (HR 0.70; p = 0.05), and this result was more pronounced on multivariable analysis (HR 0.244, 95%CI 0.130–0.457, P < 0.001). To this end, current national guidelines recommend adjuvant chemotherapy for patients with nodal metastasis.[11,12] In the present study, only 48% of patients underwent a formal lymphadenectomy, with patients who had a lymphadenectomy being more likely to receive adjuvant chemotherapy. Given the prognostic and treatment-related adjuvant implications of adequate nodal staging, regional routine lymphadenectomy should strongly be considered as a part of surgical therapy for ICC.[12]

There are several limitations that need to be considered when interpreting this data. First, given the rarity of ICC, an international, multi-institutional database that included patients from multiple decades was utilized in order to accumulate a sufficient sample size. As such, there was likely some heterogeneity regarding treatment approaches and use of adjuvant therapy. However, most patients in the study underwent surgery within the last six years. Second, like any retrospective study, unmeasured confounding and selection bias could influence the results,

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.

as patients who experience early morbidity or mortality are less likely to receive chemotherapy. To address this limitation, both multivariable and stratified analyses were performed to specifically examine the impact of adjuvant therapy among different subgroups.

In conclusion, utilizing one of the largest international, multi-institutional cohorts of patients undergoing curative hepatectomy for ICC, this study demonstrated that although adjuvant chemotherapy did not influence the long-term prognosis of all ICC patients following surgical resection, it was associated with a potential survival benefit in select subgroups of patients at increased risk for recurrence, specifically patients with advanced tumors. These findings highlight the importance of accurate pathologic staging, including a formal lymph node evaluation, in the multimodality treatment of ICC patients. Future studies will further need to better define clinicopathologic and molecular markers to identify those patients who are most likely to benefit from adjuvant systemic therapy following resection of ICC.

Acknowledgments

None.

Disclosures and funding

No conflicts of interest or funding sources to disclose.

References

1. Brown KM, Parmar AD, Geller DA. (2014) Intrahepatic cholangiocarcinoma. *Surg Oncol Clin N Am* 23:231–246. http://dx.doi.org/10.1016/j.soc.2013.10.004.
2. Shaib Y, El-Serag HB. (2004) The epidemiology of cholangiocarcinoma. *Seminars Liver Dis* 24:115–125. http://dx.doi.org/10.1055/s-2004-828889.
3. Yao KJ, Jabbour S, Parekh N, Lin Y, Moss RA. (2016) Increasing mortality in the United States from cholangiocarcinoma: an analysis of the National Center for Health Statistics database. *BMC Gastroenterol* 16:117. http://dx.doi.org/10.1186/s12876-016-0527-z.
4. Yoh T, Hatano E, Yamanaka K, Nishio T, Seo S, Taura K *et al*. (2016) Is surgical resection justified for advanced intrahepatic cholangiocarcinoma? *Liver Cancer* 5:280–289. http://dx.doi.org/10.1159/000449339.
5. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. (2014) Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. *JAMA Surg* 149:565–574. http://dx.doi.org/10.1001/jamasurg.2013.5137.
6. Ali SM, Clark CJ, Zaydfudim VM, Que FG, Nagorney DM. (2013) Role of major vascular resection in patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 20:2023–2028. http://dx.doi.org/10.1245/s10434-012-2808-2.
7. Kobayashi S, Igami T, Ebata T, Yokoyama Y, Sugawara G, Mizuno T *et al*. (2015) Long-term survival following extended hepatectomy with concomitant resection of all major hepatic veins for intrahepatic cholangiocarcinoma: report of a case. *Surg Today* 45:1058–1063. http://dx.doi.org/10.1007/s00595-014-1038-6.
8. Malde DJ, Khan A, Prasad KR, Toogood GJ, Lodge JP. (2011) Inferior vena cava resection with hepatectomy: challenging but justified. *HPB* 13:802–810. http://dx.doi.org/10.1111/j.1477-2574.2011.00364.x.
9. Spolverato G, Kim Y, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L *et al*. (2016) Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. *Ann Surg Oncol* 23:235–243. http://dx.doi.org/10.1245/s10434-015-4642-9.
10. Hyder O, Hatzaras I, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H *et al*. (2013) Recurrence after operative management of intrahepatic cholangiocarcinoma. *Surgery* 153:811–818. http://dx.doi.org/10.1016/j.surg.2012.12.005.
11. NCCN Guidelines Panel. (2017) Hepatobiliary cancers. In *NCCN clinical practice guidelines in oncology*.
12. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. (2015) Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB* 17:669–680. http://dx.doi.org/10.1111/hpb.12441.
13. Hezel AF, Zhu AX. (2008) Systemic therapy for biliary tract cancers. *Oncologist* 13:415–423. http://dx.doi.org/10.1634/theoncologist.2007-0252.
14. Jordan E, Abou-Alfa GK, Lowery MA. (2016) Systemic therapy for biliary cancers. *Chin Clin Oncol* 5:65. http://dx.doi.org/10.21037/cco.2016.10.08.
15. Valle JW, Wasan H, Johnson P, Jones E, Dixon L, Swindell R *et al*. (2009) Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - the UK ABC-01 Study. *Br J Cancer* 101:621–627. http://dx.doi.org/10.1038/sj.bjc.6605211.
16. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A *et al*. (2010) Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 362:1273–1281. http://dx.doi.org/10.1056/NEJMoa0908721.
17. Edeline J, Bonnetain F, Phelip JM, Watelet J, Hammel P, Joly J-P *et al*. (2017) Gemox versus surveillance following surgery of localized biliary tract cancer: results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. *J Clin Oncol* 35(4 Suppl):225. http://dx.doi.org/10.1200/JCO.2017.35.4_suppl.225.
18. Primrose JN, Fox R, Palmer DH, Prasad R, Mirza D, Anthoney DA *et al*. (2017) Adjuvant capecitabine for biliary tract cancer: the BILCAP randomized study. *J Clin Oncol* 35(15 Suppl):4006. http://dx.doi.org/10.1200/JCO.2017.35.15_suppl.4006.
19. Ebata T, Kamiya J, Nishio H, Nagasaka T, Nimura Y, Nagino M. (2009) The concept of perihilar cholangiocarcinoma is valid. *Br J Surg* 96:926–934. http://dx.doi.org/10.1002/bjs.6655.
20. Ebata T, Kosuge T, Hirano S, Unno M, Yamamoto M, Miyazaki M *et al*. (2014) Proposal to modify the International Union against Cancer staging system for perihilar cholangiocarcinomas. *Br J Surg* 101:79–88. http://dx.doi.org/10.1002/bjs.9379.
21. Couinaud C. (1999) Liver anatomy: portal (and suprahepatic) or biliary segmentation. *Dig Surg* 16:459–467.
22. Amini MB, Edge SB. (2018) *AJCC cancer staging manual*. New York: Springer.
23. Lafaro KJ, Cosgrove D, Geschwind JF, Kamel I, Herman JM, Pawlik TM. (2015) Multidisciplinary care of patients with intrahepatic cholangiocarcinoma: updates in management. *Gastroenterol Res Pract* 2015:860861. http://dx.doi.org/10.1155/2015/860861.
24. Rahnemai-Azar AA, Weisbrod AB, Dillhoff M, Schmidt C, Pawlik TM. (2017) Intrahepatic cholangiocarcinoma: current management and emerging therapies. *Expert Rev Gastroenterol Hepatol*. http://dx.doi.org/10.1080/17474124.2017.1309290.

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.

25. Doherty MK, Knox JJ. (2016) Adjuvant therapy for resected biliary tract cancer: a review. *Chin Clin Oncol* 5:64. http://dx.doi.org/10.21037/cco.2016.08.05.
26. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC *et al*. (2012) Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA* 308:147–156. http://dx.doi.org/10.1001/jama.2012.7352.
27. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H *et al*. (2002) Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer* 95: 1685–1695. http://dx.doi.org/10.1002/cncr.10831.
28. Miura JT, Johnston FM, Tsai S, George B, Thomas J, Eastwood D *et al*. (2015) Chemotherapy for surgically resected intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 22:3716–3723. http://dx.doi.org/10.1245/s10434-015-4501-8.
29. Horgan AM, Amir E, Walter T, Knox JJ. (2012) Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 30:1934–1940. http://dx.doi.org/10.1200/JCO.2011.40.5381.
30. de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H *et al*. (2011) Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 29:3140–3145. http://dx.doi.org/10.1200/JCO.2011.35.6519.
31. Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D *et al*. (2008) Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg* 248:84–96. http://dx.doi.org/10.1097/SLA.0b013e318176c4d3.
32. Kim Y, Spolverato G, Amini N, Margonis GA, Gupta R, Ejaz A *et al*. (2015) Surgical management of intrahepatic cholangiocarcinoma: defining an optimal prognostic lymph node stratification schema. *Ann Surg Oncol* 22:2772–2778. http://dx.doi.org/10.1245/s10434-015-4419-1.
33. Nakagawa T, Kamiyama T, Kurauchi N, Matsushita M, Nakanishi K, Kamachi H *et al*. (2005) Number of lymph node metastases is a significant prognostic factor in intrahepatic cholangiocarcinoma. *World J Surg* 29:728–733. http://dx.doi.org/10.1007/s00268-005-7761-9.
34. Ribero D, Pinna AD, Guglielmi A, Ponti A, Nuzzo G, Giulini SM *et al*. (2012) Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. *Arch Surg* 147:1107–1113. http://dx.doi.org/10.1001/archsurg.2012.1962.
35. Amini N, Ejaz A, Spolverato G, Maithel SK, Kim Y, Pawlik TM. (2014) Management of lymph nodes during resection of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: a systematic review. *J Gastrointest Surg* 18:2136–2148. http://dx.doi.org/10.1007/s11605-014-2667-1.
36. Bagante F, Gani F, Spolverato G, Xu L, Alexandrescu S, Marques HP *et al*. (2015) Intrahepatic cholangiocarcinoma: prognosis of patients who did not undergo lymphadenectomy. *J Am Coll Surg* 221: 1031–1040. http://dx.doi.org/10.1016/j.jamcollsurg.2015.09.012. e1031-1034.
37. Vitale A, Moustafa M, Spolverato G, Gani F, Cillo U, Pawlik TM. (2016) Defining the possible therapeutic benefit of lymphadenectomy among patients undergoing hepatic resection for intrahepatic cholangiocarcinoma. *J Surg Oncol* 113:685–691. http://dx.doi.org/10.1002/jso.24213.
38. Li SQ, Liang LJ, Hua YP, Peng BG, He Q, Lu MD *et al*. (2009) Long-term outcome and prognostic factors of intrahepatic cholangiocarcinoma. *Chin Med J* 122:2286–2291.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2017.06.008.

© 2017 International Hepato-Pancreato-Biliary Association Inc. Published by Elsevier Ltd. All rights reserved.

Downloaded for Anonymous User (n/a) at Centro Hospitalar Lisboa Central from ClinicalKey.com by Elsevier on February 20, 2018.
For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.